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| 10/594,517 | 09/28/2006 | Yoshiko Kubo | 296115US0PCT | 1811 |

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| EXAMINER | |
|---|---|
| BROWN, COURTNEY A | |

| ART UNIT | PAPER NUMBER |
|---|---|
| 1617 | |

| NOTIFICATION DATE | DELIVERY MODE |
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| 09/16/2010 | ELECTRONIC |

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

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| Office Action Summary | Application No. | Applicant(s) | |
|---|---|---|---|
| | 10/594,517 | KUBO ET AL. | |
| | Examiner | Art Unit | |
| | COURTNEY BROWN | 1617 | |

*-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --*

**Period for Reply**

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

1)☒ Responsive to communication(s) filed on *03 May 2010*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

4)☒ Claim(s) *1-17* is/are pending in the application.

4a) Of the above claim(s) *9 and 16* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10-15 and 17* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

**Application Papers**

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☒ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *9/28/06*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

## DETAILED ACTION

### *Election/ Restriction*

The Examiner acknowledges receipt of Applicant's response to the restriction requirement filed on May 3, 2010. Applicant elected with traverse Group II, claims 1-8,10-15 and 17 drawn to a fine dispersion of 1-cyclopropyl-8- methyl-7-[5-methyl-6-(methylamino)-3-pyridinyl]-4-oxo- 1,4-dihydro-3- quinolinecarboxylic acid and a process for producing a fine dispersion of 1 -cyclopropyl- 8-methyl- 7- [ 5-methyl-6-(methylamino)-3-pyridinyl] -4- oxo- 1,4-dihydro-3-quinolinecarboxylic acid. Applicant traversed on the grounds that that the Office has not provided any indication that the contents of the claims interpreted in light of the description was considered in making the assertion of a lack of unity and therefore has not met the burden necessary to support the assertion. Applicant argues that the Office has not considered the relationship of the inventions of Groups I-II with respect to MPEP §806.03 nor paragraph (b) of Annex B of the Administrative Instructions Under the PCT. The Examiner respectfully disagrees with this viewpoint. The inventions listed as Groups I and II do not relate to a single general inventive concept under PCT Rule 13.1 because, under PCT Rule 13.2, they lack the same or corresponding special technical features for the following reasons: the common technical feature in all groups is a fine dispersion of less than 1000 nm in particle size. This element does not constitute a special technical feature under PCT Rule 13.2

because the element is shown in prior art. US Patent 5,510,118 teaches a process of preparing nanoparticulate drug substances comprising the steps of: preparing a premix of the drug substance and a surface modifier, and subjecting the premix to mechanical means to reduce the particle size of the drug substance, the mechanical means producing shear, impact, cavitation and attrition wherein said process produces a particle size of less than about 400 nm (see claim 1 of US Patent 5,510,118). The invention of the instant application lacks a special corresponding technical feature and does not make a contribution to the prior art. Therefore, the claims cannot be said to have unity of invention. For these reasons, the restriction requirement is repeated and hereby expressly made **final**.

***Status of Claims***

Claims 1-17 are pending in the application. Claims 9 and 16 have been withdrawn as being directed to a non-elected invention. Claims **1-8,10-15 and 17** are being examined for patentability.

***Priority***

Applicant's claim for the benefit of a prior-filed application under 35 U.S.C. 119(e), 119(a-d), or under 35 U.S.C. 120, 121, or 365(c) is acknowledged. This application is a 371 of PCT/JP05/05736 filed on March 28, 2005.

***Information Disclosure Statement***

The Information Disclosure Statements (IDS) submitted on September 28, 2006 has been considered by the examiner.

***Abstract Objections***

The abstract of the disclosure is objected to because of undue length. The abstract should not be more than 150 words and should be a single paragraph. Correction is required. See MPEP § 608.01(b).

Applicant is reminded of the proper content of an abstract of the disclosure.

A patent abstract is a concise statement of the technical disclosure of the patent and should include that which is new in the art to which the invention pertains. If the patent is of a basic nature, the entire technical disclosure may be new in the art, and the abstract should be directed to the entire disclosure. If the patent is in the nature of an improvement in an old apparatus, process, product, or composition, the abstract should include the technical disclosure of the improvement. In certain patents, particularly those for compounds and compositions, wherein the process for making and/or the use thereof are not obvious, the abstract should set forth a process for making and/or use thereof. If the new technical disclosure involves modifications or alternatives, the abstract should mention by way of example the preferred modification or alternative.

The abstract should not refer to purported merits or speculative applications of the invention and should not compare the invention with the prior art.

Where applicable, the abstract should include the following:
(1) if a machine or apparatus, its organization and operation;
(2) if an article, its method of making;
(3) if a chemical compound, its identity and use;
(4) if a mixture, its ingredients;
(5) if a process, the steps.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

**Claims 1-8,10-15 and 17 are rejected under 35 U.S.C. 103(a) as being unpatentable over Bosch et al. (US Patent 5,510,118) in view of Yamakawa et al. (*Journal of Controlled Release*, 86(2003) 101-103).**

***Applicant's Invention***

Applicant is claiming a process for producing a fine dispersion of a poorly soluble drug, comprising the steps of: suspending said poorly soluble drug in a liquid containing no deflocculant to obtain a suspension; introducing said suspension into a high-

pressure homogenizer to subject the same to high-pressure treatment to obtain a dispersion; and adding a deflocculant to [[the]] said dispersion to deagglomerate aggregated particles contained therein.

***Determination of the scope and the content of the prior art (MPEP 2141.01)***

Bosch et al. teach a process of preparing nanoparticulate drug substances comprising the steps of: preparing a premix of the drug substance and a surface modifier, and subjecting the premix to mechanical means to reduce the particle size of the drug substance, the mechanical means producing shear, impact, cavitation and attrition (abstract). Bosch et al. teach that the drug substance must be poorly soluble and dispersible in at least one liquid medium (column 4,lines 56-57) and can selected from a variety of know classes of drugs including anti-arrhythmic, antibiotics, antimycobacterial agents, antiviral agents and astringents (column 5, lines 1-42). Suitable surface modifiers are selected from various polymers, low molecular weight oligomers, natural products and surfactants such as carboxymethylcellulose calcium, hydroxypropylmethylcellulose phthalate and polyvinylpyrrolidone (column 5, line 45 bridging to column 6, lines 1-29). Bosch et al. teach that said particle size refers to a number average particle size of less than about 400 nm wherein at least 90% of the particles have a weight average particle size of less than about 400 nm (column 6, lines 37-54). Bosch et al. teach that the coarse drug substance can be added to a liquid medium to form a premix (column 7, lines 51-53) and then transferred to a

mocrofulidizer (high-pressure homogenizer of instant application) and circulated continuously first at a low pressure and then at a maximum capacity of about 3,000 to 30,000 psi until the desired particle size reduction is achieved (column 7, lines 63-67). Bosch et al. teach that the surface modifier, if not present in the premix, must be added to the dispersion after attrition (column 8, lines 16-18).

***Ascertainment of the difference between the prior art and the claims (MPEP 2141.02)***

The difference between the invention of the instant application and that of Bosch et al. is that Bosch et al. do not expressly teach a process for producing a fine dispersion of 1-cyclopropyl-8-methyl-7-[5-methyl-6- (methylamino)-3-pyridinyl]-4-oxo-1,4-dihydro-3-quinolinecarboxylic acid (i.e., T-3912) . However, it is known in the prior art that T-3192 has low solubility. For example, Yamakaw et al. teach a study evaluating the combined use of polyvinylpyrrodidone and T-3192 in order to obtain a stable liquid formulation of T-3912 (abstract).

***Finding of prima facie obviousness***

***Rationale and Motivation (MPEP 2142-2143)***

It would have been obvious to one of ordinary skill in the art at the time of invention to combine the teachings of Bosch et al. and Yamakaw et al. to devise a

process for producing a fine dispersion of 1-cyclopropyl-8-methyl-7-[5-methyl-6-(methylamino)-3-pyridinyl]-4-oxo- 1,4-dihydro-3-quinolinecarboxylic acid (i.e., T-3912). Yamakaw et al. teach that T-3912 is only sparingly soluble in water: at pHs of 6, 7 and 8, and that its solubility is 1, 1.5 and 8.4 µg/ml, respectively. Taking this into account, in attempting to extend its use in topical application, in particular, for ophthalmic formulations, Yamakaw et al. teaches that the solubility of T-3912 had to be improved. Further, Bosch et al. teach that poorly water soluble drugs tend to have poor bioavailability and be eliminated from the gastrointestinal tract before being absorbed into the circulation (column 1, lines 18-22). One skilled in the art at the time the invention was made would have been motivated to combine the teachings of Bosch et al. and Yamakaw et al. and produce a fine dispersion of T-3912 with the expected benefit of increasing the rate of dissolution of T-3912 by decreasing the particle size (see column 1, lines 25-28 of Bosch et al.) which results in increased bioavailability of T-3912. Therefore, the claimed invention as a whole would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made because every element of the invention has been fairly suggested by the cited reference.

In light of the forgoing discussion, the Examiner concludes that the subject matter defined by the instant claims would have been obvious within the meaning of 35 USC 103(a).

From the teachings of the references, it is apparent that one of ordinary skill in the art would have had a reasonable expectation of success in producing the claimed

invention. Therefore, the invention as a whole was *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references, especially in the absence of evidence to the contrary.

***Conclusion***

The claims remain rejected.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR Only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Courtney Brown, whose telephone number is 571-270-3284. The examiner can normally be reached on Monday-Friday from 8 am to 4:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Fereydoun Sajjadi can be reached on 571-272-3311. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Patent Examiner
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/Ernst V Arnold/
Primary Examiner, Art Unit 1613